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(19) Europäisch s Patentamt
European Patent Office
Office europé n des br vets

(11) Publication number: **0 161 4 9 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **85104478.4**

(22) Date of filing: **12.04.85**

(51) Int. Cl.⁴: **C 07 D 491/056**, A 61 K 31/47

(30) Priority: **17.04.84 JP 77005/84**

(43) Date of publication of application: **21.11.85 Bulletin 85/47**

(84) Designated Contracting States: **BE CH DE FR GB IT LI NL SE**

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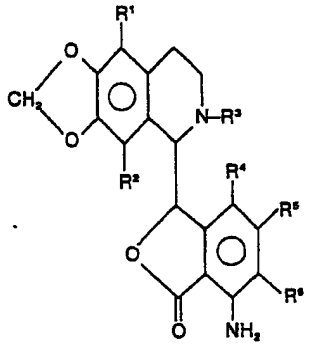
(54) Process for preparation of aminophthalidelsoquinolines.

(57) Disclosed herein is an improved process for preparing 1RS-3'-RS epimer of aminophthalidelsoquinolines represented by the general formula (I):



(I)

wherein R^1 and R^2 independently represent hydrogen atom or a lower alkoxy group, R^3 is a lower alkyl group, and R^4, R^5 and R^6 independently represent a lower alkoxy group. The improvement comprises, in the first step of reacting trihydroxybenzoic acids with dialkyl sulfates, maintaining the pH of aqueous reaction media in the range of from 8.5 to 11, inclusive, by the addition of a caustic alkali.

EP 0 161 499 A1

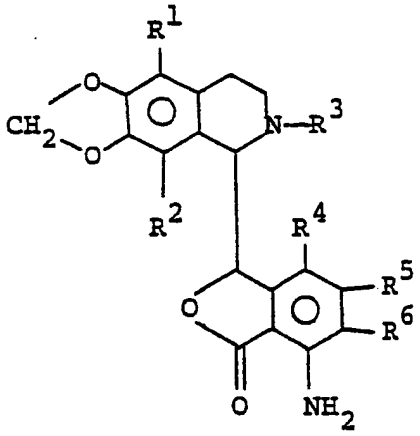
PROCESS FOR PREPARATION OF AMINOPHTHALIDEISOQUINOLINES

FIELD OF THE INVENTION

This invention relates to a process for preparing aminophthalideisoquinolines, hereinafter referred to as amino compounds, and more particularly, to a process for preparation of the amino compounds from a trihydroxybenzoic acid as a starting material.

BACKGROUND OF THE INVENTION

Amino compounds represented by the following general formula (I):



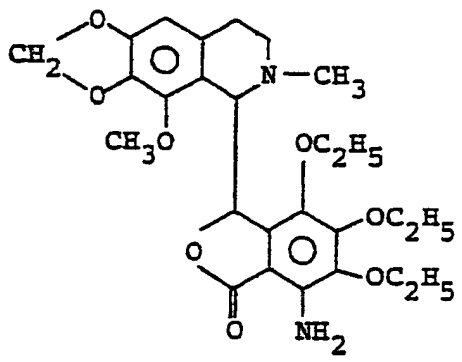
(I)

wherein R^1 and R^2 independently represent hydrogen atom or a lower alkoxy group, R^3 represents a lower alkyl group, and R^4, R^5 and R^6 independently represent a lower alkoxy group,

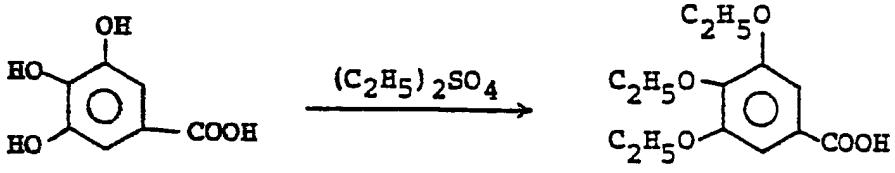
have two epimers, that is, 1RS-3'RS epimer (hereinafter referred to as "A-mer") and 1RS-3'SR epimer (hereinafter referred to as "B-mer"). The A-mer shows excellent properties as a drug for the treatment of liver diseases or as an anti-allergic drug.

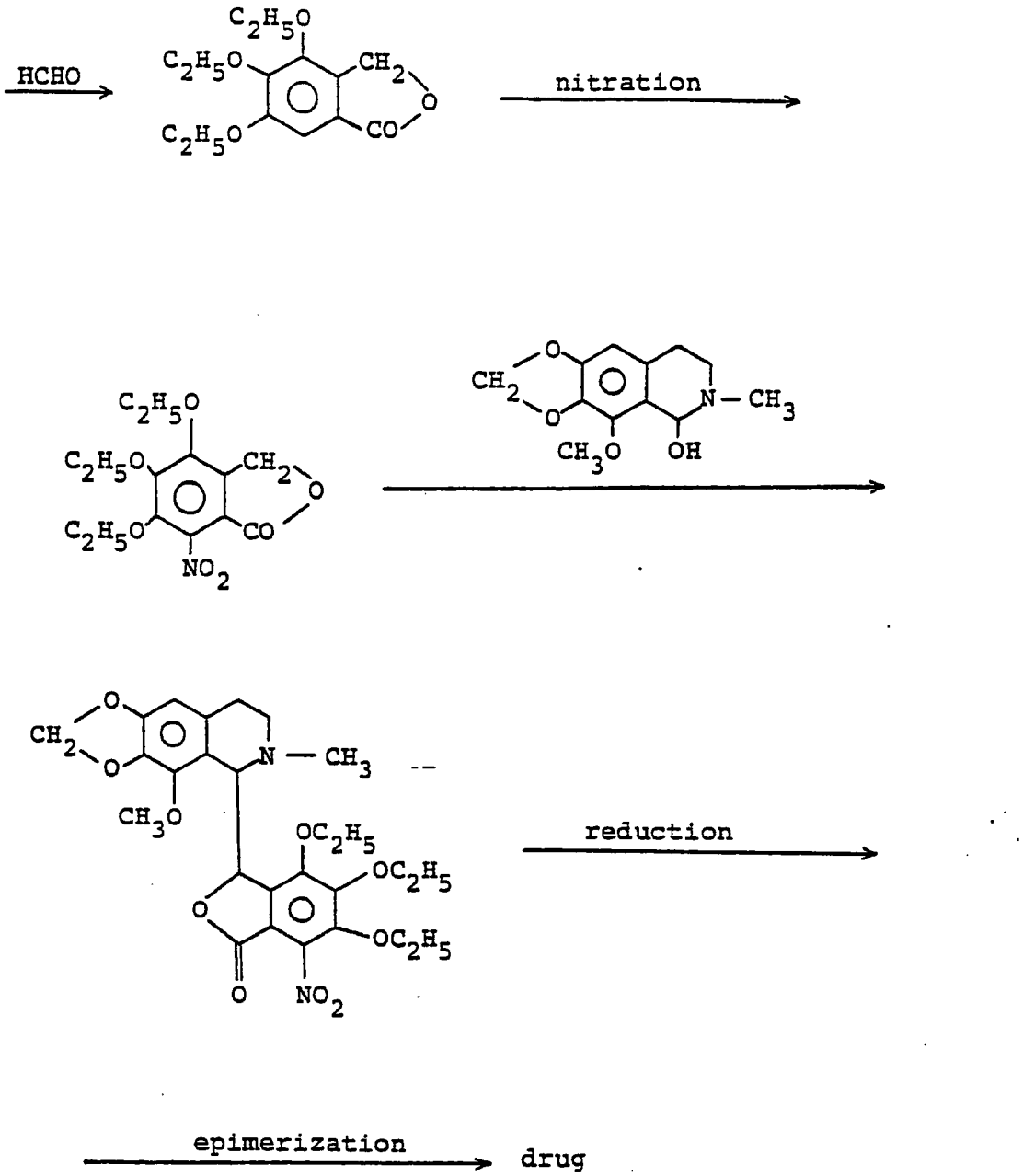
Generally, the drug can be prepared from a trihydroxybenzoic acid as a starting material. The reaction process comprises six steps and, therefore, the yield of each step should be improved to obtain a sufficiently high total yield of the end product in order to reduce the cost of manufacture.

For example, the amino compound represented by the following formula:



may be synthesized by the following reaction route:





The invention provides an improvement in the step of preparation of trialkoxybenzoic acid from trihydroxybenzoic acid with dialkyl sulfate.

Generally, trialkoxybenzoic acid may be prepared by reacting trihydroxybenzoic acid with dialkyl sulfate in an aqueous caustic alkali to obtain an alkyl ester of the trialkoxybenzoic acid which is then hydrolyzed to an alkali metal salt of the trialkoxybenzoic acid, followed by acidifying the salt, as given, for example, in Ann. Chem., 763, 109-120 (1972).

In this process, however, the product of the reaction of trihydroxybenzoic acid with dialkyl sulfate contains so much amount of by-products, that the solid mass obtained on acidifying the reaction mixture becomes gummy and very difficult to be handled. For obtaining better powdery crystals, it has been required that the acid precipitation should be carried out after refining the raw product by any means, for example, adsorption in an aqueous alkaline solution.

It is an object of the present invention to provide an improved process for obtaining a better powdery crystal of a trialkoxybenzoic acid with a high purity in the acid precipitation of the reaction mixture.

SUMMARY OF THE INVENTION

The present inventor has now found that a reaction of trihydroxybenzoic acid with dialkyl sulfate at the specified pH range effectively and significantly inhibits the formation of by-products resulting in better powdery crystals with a high yield in the acid precipitation after hydrolysis of the alkyl ester of trialkoxybenzoic acid.

The process for preparing amino compounds represented by the above defined formula (I) according to the invention comprises synthesizing the amino compounds from trihydroxybenzoic acid in the above specified reaction route. The process is characterized in that the reaction of the trihydroxybenzoic acid with a dialkyl sulfate is performed in an aqueous medium while maintaining the pH in the range of from 8.5 to 11 with the aid of a caustic alkali.

DESCRIPTION OF THE INVENTION

The invention will be fully described hereinbelow.

The "lower alkoxy or alkyl group" represented by R^1 to R^6 of the general formulae (I) to (III) includes those having one to five carbon atoms, for example, methyl, ethyl, propyl, butyl, heptyl, or methoxy, ethoxy, or the like.

Preparation of trialkoxybenzoic acids

Starting materials which may be used in the reaction of trihydroxybenzoic acid with dialkyl sulfate are generally 3,4,5-trihydroxybenzoic acid and a dialkyl (C_1-C_5) sulfate, such as dimethyl sulfate, diethyl sulfate, di-n-propyl sulfate, di-n-butyl sulfate and the like.

According to the invention, the reaction is carried out in an aqueous caustic alkali. The amount of the aqueous medium used is usually 4 to 10 times by weight, based on the weight of the trihydroxybenzoic acid. Caustic alkalis which may generally be used include sodium hydroxide and potassium hydroxide.

The reaction is carried out at a temperature in the range of from 60 to 95°C, preferably from 70 to 95°C. At a too low temperature the reaction rate will be too slow, in

other words, the reaction cannot efficiently proceed, while, on the contrary, too high temperatures will give more undesirable by-products. The reaction period may ordinarily be about 1 to 10 hours.

The reaction may generally be performed batchwise. For example, the dialkyl sulfate may be dropwise added to a base solution containing the other starting material, i.e. trihydroxybenzoic acid, under reaction conditions. Usually, the dialkyl sulfate may be used in an amount of 4 to 7 times by mole, preferably 4.5 to 6 times by mole, based on the amount of the trihydroxybenzoic acid. Smaller amounts of the dialkyl sulfate will be unpractical since the reaction could not be completed and, therefore, intermediates or others would remain in the reaction mixture.

According to the invention, the pH of the reaction system should be maintained in the range of from 8.5 to 11, preferably from 9 to 10.5. At a pH lower than the range, a desirable trialkoxybenzoic acid cannot be obtained with a high yield and, moreover, only gummy mass with a low purity will be collected in the subsequent acid precipitation. On the other hand, an effective reaction cannot be expected since larger amounts of dialkyl sulfate may decompose at higher pH values.

In order to maintain the pH in the predetermined range, for example, when a batchwise reaction is carried out by adding dropwise a dialkyl sulfate to a base solution

containing trihydroxybenzoic acid, the pH can usually be adjusted by the addition of an aqueous solution of sodium hydroxide depending on the addition of the dialkyl sulfate while measuring the pH of the system. Thus, the pH in the reaction system is lowered as the reaction of the dialkyl sulfate proceeds. According to the invention, the pH of the reaction system is adjusted with the aid of a caustic alkali so as to fall within the specified range.

Alkyl esters of trialkoxybenzoic acid produced in the abovementioned reaction are then subjected to hydrolysis to obtain alkali salts of the trialkoxybenzoic acid. The salts are subsequently subjected to acid precipitation to collect crystals of the trialkoxybenzoic acid.

Hydrolysis is usually performed at a pH higher than 11 with a caustic alkali and at a temperature in the range of from 80 to 100°C for about 0.5 to 5 hours.

Acid precipitation is carried out until the pH of the reaction mixture is 4 or lower, preferably 3.5 or lower. Sulfuric acid or hydrochloric acid is preferably utilized.

After acid precipitation, deposited crystals may be collected by filtering the mixture according to any conventional manner. According to the present invention, the crystals are obtained in the form of powder, which can be easily handled. Filtration is ordinarily performed at 40°C or higher. Too low temperatures are not practical since inorganic salts may be deposited and contaminate the product.

The collected crystals of trialkoxybenzoic acid may be washed, if necessary, for example, by suspending once to three times in warm water of 30°C or higher, preferably 70°C or higher.

In one preferred embodiment of the invention, the aforementioned procedures may be performed in the following manner: a trihydroxybenzoic acid is charged in water and a caustic alkali is added thereto; the resulting homogeneous solution is heated under reaction conditions; simultaneously, a predetermined amount of a dialkyl sulfate is fed while the pH of the reaction mixture is maintained in the specified range; after reaction, the caustic alkali is further added to increase the pH of the reaction mixture which is thus subjected to hydrolysis under heating; finally, the mixture is subjected to acid precipitation.

According to the aforementioned reaction in the invention, desirable products can be produced with an improved yield and less production of by-products, and further, powdery crystals may be collected in the subsequent acid precipitation step, by performing the reaction of a trihydroxybenzoic acid with a dialkyl sulfate at a pH in the specified range.

Preparation of trialkoxyphthalides

The trialkoxybenzoic acid obtained in the above procedures is then reacted with formaldehyde to prepare trialkoxyphthalide.

The reaction is usually carried out in an aqueous solution of an acid, such as, for example, sulfuric acid or

hydrochloric acid, preferably in an aqueous solution of 5 to 40% by weight of sulfuric acid. Formaldehyde is used in the form of an aqueous solution or gas. An aqueous solution of formaldehyde, if used, may contain a small amount of a stabilizer, for example, methanol or the like. The amount of formaldehyde used is 2 to 60 times by mole, preferably 3 to 20 times by mole, based on the amount of the trialkoxybenzoic acid used.

The reaction may well proceed when 0.25 to 3 times by weight, preferably 0.9 to 1.4 times by weight, based on formaldehyde, of acetic acid is present.

The reaction temperature may generally be in the range of from 50 to 120°C, preferably from 70 to 110°C, and the reaction period may usually be 2 to 60 hours, preferably 4 to 30 hours. The reaction is usually carried out batchwise in a conventional reaction vessel with a stirrer.

The trialkoxyphthalide produced in the reaction is collected from the mixture. Generally, the reaction mixture is cooled to 0 to 50°C and the deposited crystals are filtered out. The crystals are then washed with an aqueous alkaline solution to remove unreacted materials contained in the crystals.

An aqueous alkaline solution which may be used is an aqueous solution of 0.5 to 30% by weight, preferably 1 to 5% by weight, of e.g. solium hydroxide, potassium hydroxide, sodium carbonate or ammonia. Washing with an alkali is usually performed by suspension under conditions, for example, at 60 to 10°C for 0.5 to 3 hours.

Preparation of trialkoxynitrophthalides

The trialkoxyphthalide is then subjected to nitration to obtain a trialkoxynitrophthalide.

One example of nitration procedures which may generally be utilized is a method using a nitrate salt, such as cupric nitrate and zinc nitrate, but the invention is not limited to this method.

In such a method, there may generally be utilized, as a solvent, an acid anhydride, such as acetic anhydride, trifluoroacetic anhydride and propionic anhydride, or a lower fatty acid, such as acetic acid and trifluoroacetic acid. In combination with such a solvent, there may also be used an inert solvent, such as haloalkanes, for example, dichloromethane, carbon tetrachloride or dichloroethane, nitroalkanes, for example, nitromethane or nitroethane, and nitrobenzene, etc. The solvent may usually be used in an amount of 2 to 20 times by weight, preferably 3 to 6 times by weight, based on the amount of the trialkoxyphthalide used.

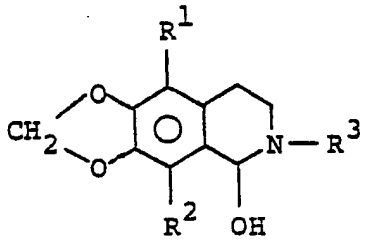
The nitration reaction is generally carried out at 0 to 120°C, preferably 20 to 60°C, for 0.5 to 4 hours. The amount of a nitrating agent used, namely nitrate salt, is generally 0.8 to 5 times by mole, preferably 1 to 2 times by mole, based on the amount of the trialkoxyphthalide used.

After reaction, the trialkoxynitrophthalide produced is usually deposited by adding water to the reaction mixture followed by filtration to collect the crystals.

Other methods, for example, utilizing a mixed acid of nitric acid and sulfuric acid as a nitrating agent can also be used in the nitration step of the invention.

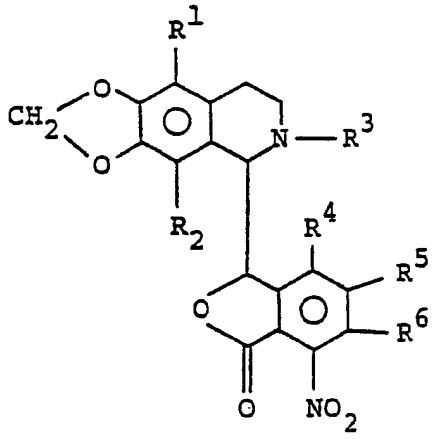
Preparation of nitrophthalideisoquinolines

The trialkoxynitrophthalide is then subjected to condensation reaction with an isoquinoline represented by the following general formula (III):



(III)

wherein R^1 to R^3 are as defined above, to prepare a nitrophthalideisoquinoline represented by the following general formula (II):



(II)

wherein R^1 to R^6 are as defined above.

The condensation is generally carried out at a temperature in the range of from 20 to 100°C, preferably from 40 to 80°C, for approximately 1 to 3 hours in an aliphatic alcohol as a solvent, for example, methanol, ethanol, propanol or butanol. The reaction rate will unsuitably be slow at a lower temperature, while undesirable decomposition of the starting material, i.e. isoquinoline, may occur if the temperature is too high.

In the condensation reaction, either A-mer or B-mer of the product, i.e. nitrophthalideisoquinoline, can be produced, depending on the difference in the configuration, RS or SR, of hydrogen atom at the condensing position, that is, of hydrogen atom bonded to the carbon atom at 1-position of the isoquinoline or 3'-position of the nitrophthalide. Thus, there may usually be obtained a mixture of A-mer and B-mer of the product. Generally, the longer is the reaction period, the higher is the ratio of A-mer but the lower is the yield of the product. In the present invention, however, the proportion of A-mer in the product produced in this condensation step is not especially limited, since the produced B-mer can be well converted into A-mer in the later step described hereinbelow. The proportion (content) of A-mer in the product may usually be in the range of approximately 20 to 80% by mole.

The amount of the isoquinoline used may generally be in the range of from 0.8 to 1.2 times by mole, preferably 0.9 to 1.0 times by mole, based on the amount of the nitrophthalide used. Smaller amount results in a low yield of the product, i.e. nitrophthalideisoquinoline, while an amount more than the upper limit may cause undesirable decomposition of the isoquinoline.

Generally, the crystalline product can easily be collected by crystallization by cooling or water dilution of the reaction mixture at the end of this condensation step.

Reduction and epimerization

The nitrophthalideisoquinoline is further treated to prepare A-mer of the amino compound represented by the general formula (I), which is useful for a drug, by either (A) reduction followed by epimerization or (B) epimerization followed by reduction. The procedures (A) are more preferred since A-mer of the amino compound may be obtained with a higher yield.

Reduction methods which may be utilized in the invention include: (i) reduction using a metal borohydride as a reducing agent, such as $NaBH_4$, $LiBH_4$, $NaBH_3CN$, $NaBH_2S_3$, $NaBH(OCH_3)_3$, $NaBH_3(OH)$, KBH_4 and the like, in the presence of a catalyst selected from the group consisting of metals of the IB and VIII groups, such as Cu, Ag, Ni, Pd and Rh, and salts thereof, such as hydrochlorides, sulfates and acetates; (ii) reduction using as a reducing agent a combination of a metal, such as Sn, Fe, Zn and the like, or a compound thereof with hydrochloric acid; (iii) catalytic hydrogenation using a platinum group metal, such as Pd and Pt, or a compound

thereof as a catalyst; and (iv) reduction using $LiBH_4$ or $NaBH_2S_3$ as a reducing agent in the absence of any catalyst.

These reduction procedures are generally carried out at a temperature in the range of from 0 to 100°C, preferably from 20 to 60°C, although the temperature can slightly value depending on each procedure. Higher temperatures may yield a larger amount of by-products. On the contrary, a lower temperature will result in a slower reaction rate and, therefore, the desired amino compounds cannot efficiently be obtained. The reaction period is usually 10 minutes to 4 hours.

The reduction may generally be carried out in a solvent which may slightly vary depending on each procedure, for example, an aliphatic alcohol, such as methanol, ethanol and propanol, an ether, such as diglyme and tetrahydrofuran, an aliphatic ketone, such as acetone and methyl ethyl ketone, a water-miscible organic solvent, such as dimethylformamide and dimethyl sulfoxide, an aqueous solution thereof, or the like. When a metal borohydride is used as a reducing agent, an aliphatic alcohol may be particularly preferred since the mixture can immediately be subjected to the subsequent epimerization step described below. The solvent may generally be used in an amount of 2 to 50 times by weight, preferably 3 to 20 times by weight, based on the nitrophthalideisoquinoline of the general formula (II) used. The nitrophthalideisoquinolines may also be supplied in the form of a solution in e.g. acetone or acetic acid.

The amino compound of the general formula (I) can be separated and collected from the reduced mixtures: for

example, the reaction mixture can be subjected to extraction at a neutral or alkaline pH with an organic solvent in which the amino compound can be dissolved, such as halogenated hydrocarbons. Thus, the amino compound can be collected in an organic phase. When any solid catalyst is present in the reaction mixture, the solid may preliminarily be either filtered out or dissolved, if necessary.

The epimerization of the aminophthalideisoquinoline can generally be performed in an aliphatic alcohol in the presence of an alkali, while the epimerization of the nitrophthalide-isoquinoline, according to the procedure (B) given above, can be performed by heating without alkali in the same solvent.

The aliphatic alcohols which may be used include those having 1 to 5 carbon atoms, such as methanol, ethanol, propanol and butanol. The solvent may also contain some water. The solvent may usually be used in an amount of 3 to 20 times by weight based on the amount of the amino compound of the general formula (I) used.

The alkali which may be used is, for example, an alkali hydroxide, such as sodium hydroxide, potassium hydroxide and barium hydroxide, an alkali alkoxide, such as sodium alcoholate, or the like. The alkali may be used in a concentration of 1 to 5% by weight, preferably 2 to 5% by weight. Lower concentrations will cause a slow reaction rate while higher concentrations may result in a low yield. The amount of the alkali used is 0.4 to 3 times by mole, preferably 0.9 to 2 times by mole, based on the amount of B-mer to be epimerized.

The epimerization may generally be performed at a temperature in the range of from 20 to 100°C, preferably from 50 to 80°C. Lower or higher temperatures cannot result in a desirably high content of A-mer. The epimerization period may vary depending on the temperature and the concentration of alkali used, but is generally 2 to 20 hours.

The epimerization of the amino compound may generally be carried out by adding the material into a solvent containing a predetermined amount of an alkali and treating the mixture under predetermined conditions with stirring. In these conditions, although B-mer can be dissolved, A-mer may hardly be dissolved and remains as crystals. Therefore, the mixture can be treated either directly in the form of a slurry or after preliminarily separating the precipitated A-mer. Further, since the epimerized mixture contains both the deposited A-mer and the dissolved B-mer, the desired crystal of A-mer can be obtained by solid-liquid separation of the mixture.

The A-mer of the amino compound can be recovered with a high purity by a simple filtration of the mixture after the epimerization. Thus, when the epimerization is performed after reduction, a highly pure A-mer of the amino compound of the general formula (I), which may be used as a bulk of a drug, can directly be collected from the mixture after the procedures.

According to the present invention, compounds which are useful for a drug for the treatment of liver diseases or allergies can be prepared advantageously and industrially from a trihydroxybenzoic acid.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The invention will be fully and clearly illustrated with the following examples. These examples should be construed as illustration only but not as limiting. Various modifications and variations can be made by those skilled in the art and such modifications and variations will be included within the scope of the invention.

EXAMPLE 1

Into a 30 liter reaction vessel provided with a stirred and a heater, 925 g (4.916 mole) of 3,4,5-trihydroxybenzoic acid and 6,000 g of water were charged. After purging by nitrogen gas, 2,060 g (12.86 mole of NaOH) of a 25% aqueous solution of sodium hydroxide was added at a temperature of 15°C or lower under stirring to completely dissolve 3,4,5-trihydroxybenzoic acid. The resulting mixture had a pH of 10.5.

After 1,060 g (6.88 mole) of diethyl sulfate was added at a temperature of 15°C or lower, the mixture was heated upto 80°C over a time period of 30 minutes while adding a 25% aqueous solution of sodium hydroxide so that the pH of the mixture was maintained at 9 to 9.5. Then, 2,835 g (18.39 mole) of diethyl sulfate and 2,750 g of a 25% aqueous solution of sodium hydroxide (17.17 mole of NaOH) were separately added dropwise at 80 to 90°C over one hour so that the pH was maintained at 9 to 9.5. Thereafter, the mixture was reacted at 90°C for an additional half one hour.

After the reaction time of 30 minutes, 2,560 g of a 25% aqueous solution of sodium hydroxide (15.98 mole of NaOH) was added to the reaction mixture, so that the pH was adjusted up to 11.5. The mixture was hydrolyzed under reflux at 90 to 95°C for 3 hours. After hydrolysis, 2,000 g of 50% sulfuric acid (10.2 mole of H_2SO_4) was added at 70°C so that the pH was adjusted to 3 for acid precipitation. Deposited crystals were filtered at 40°C, washed with water, filtered again and dried to collect the crystal of 3,4,5-triethoxybenzoic acid.

The yield based on 3,4,5-trihydroxybenzoic acid and the purity of the obtained crystal are shown in Table 1 below.

COMPARATIVE EXAMPLES 1 AND 2

In the procedures of Example 1, the addition rate of an aqueous solution of sodium hydroxide was changed so that the pH of the reaction mixture was maintained at a value shown in Table 1 in the reaction of 3,4,5-trihydroxybenzoic acid with diethyl sulfate. The results are shown in Table 1.

Table 1

	pH Range	Yield (%)	Purity (%)	Crystal Form
Example 1	9 - 9.5	90	95	Powder
Comparative Example 1	3	48	55	Gummy
Comparative Example 2	7.3-8.0	68	68	Gummy

EXAMPLES 2 - 4

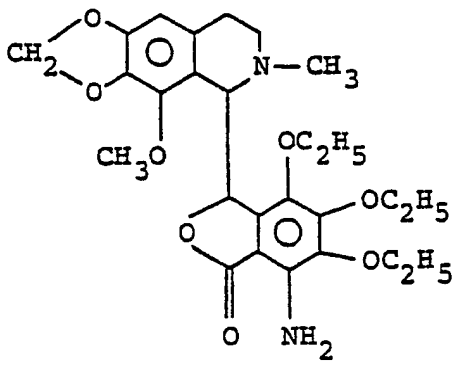
The procedures of Example 1 were repeated except that a pH range was changed as shown in Table 2. The results are shown in Table 2.

Table 2

	pH Range	Yield (%)	Purity (%)	Crystal Form
Example 2	10.0-10.4	92	96	Powder
Example 3	10.5-10.8	89	93	Powder
Example 4	8.5-8.7	80	83	Powder

EXAMPLE 5: PREPARATION OF AMINOPHTHALIDEISOQUINOLINE

Tritoqualine which is included in the amino compounds of the general formula (I) was prepared from 3,4,5-triethoxybenzoic acid produced in Example 1.



Preparation of 4,5,6-triethoxyphthalide

Into a 2 liter reaction vessel provided with a stirrer and a heater, there were charged 203.5 g (0.8 mole) of 3,4,5-triethoxybenzoic acid, 519 g (6.39 mole of HCHO) of an aqueous solution of 37% by weight of formaldehyde, 204.1 g of 98% by weight of sulfuric acid, 211 g of glacial acetic acid and 469 g of water, and the mixture was reacted at 95°C under stirring for 14 hours.

After reaction, the reaction mixture was cooled to 40°C to solidify the oily components in the mixture. After the deposited cakes were filtered and washed with water, the cakes were washed by suspending in 800 ml of an aqueous solution of 3% by weight of ammonia at 30°C for one hour. Suspension washing was further carried out at 30°C for one hour in 600 ml of an aqueous solution of 80% by volume of methanol. After filtration and drying there was obtained 125.8 g of 4,5,6-triethoxyphthalide.

High performance liquid chromatography showed a purity of 99% and a yield of 59% of the crystal.

Preparation of 4,5,6-triethoxy-7-nitrophthalide

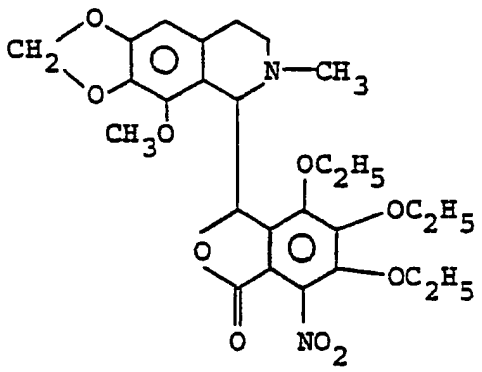
There was added 53.2 g (0.20 mole) of 4,5,6-triethoxyphthalide into 204 g of acetic anhydride. After the mixture was charged in a reaction vessel, 67.6 g (0.28 mole) of cupric nitrate trihydrate was added over one hour under stirring while maintaining the temperature of the reaction mixture at 30°C. After the addition, the reaction mixture was stirred at 30°C for one hour and then poured into 800 g of ice water.

The mixture was stirred at room temperature for one hour. Deposited crystals were filtered out, throughly washed with water, and dissolved in 300 ml of methanol under heating at 40°C to remove insolubles. After distilling out 240 ml of methanol from the filtrate under reduced pressure, 30 ml of water was added to the residual solution. The deposited crystals were filtered out and dried. There was obtained 40.4 g of 4,5,6-triethoxy-7-nitrophthalide with a yield of 65%.

Preparation of 2-methyl-6,7-methylenedioxy-8-methoxy-1-[4,5,6-triethoxy-7-nitrophthalidyl-(3)]-1,2,3,4-tetrahydroisoquinoline

Into a glass reaction vessel, there were charged 31.1 g (0.1 mole) of 4,5,6-triethoxy-7-nitrophthalide, 23.7 g (0.1 mole) of cotarnine and 80 ml of methanol. Condensation was carried out under stirring at 60°C for 2 hours.

After reaction, 50 ml of water was added to the reaction mixture and cooled at 20°C. There was deposited the end product represented by the following formula:



There was obtained the product with a yield of 75% based on cotarnine. The product contained 46% of A-mer and 54% of B-mer.

Preparation of tritoqualine

Into a glass reaction vessel, 26.5 g (0.05 mole) of the product obtained above, 1.76 g of cupric sulfate and 80 ml of methanol were charged, and a solution of 3.8 g (0.1 mole) of sodium borohydride in 35 ml of methanolic solution of 1N sodium hydroxide was dropwise added at 35°C under stirring over one hour. Stirring was continued at the same temperature for an additional one hour to react. Analysis of the product in the resultant mixture showed the conversion rate of 98% and selectivity of 98%.

After adding 50 ml of 35% hydrochloric acid to the mixture obtained above in order to decompose the remaining excess sodium borohydride, copper was oxidized by blowing air thereinto. Then, 60 ml of 28% aqueous ammonia and 50 ml of water were added to convert the amino compound into the free form, while copper formed an amine complex with ammonia. The mixture was then extracted with 160 ml of dichloromethane. Thus, the amino compound was well extracted into the organic phase, while the metal components remained in the water layer, not giving any deposit. In these procedures, methanol was totally distributed into the water layer while the product was recovered into the organic phase with a yield of approximately 100%.

To the obtained solution of the amino compound in dichloromethane, 480 ml of methanol was added and the solvent was distilled off to concentrate to the solvent volume of 100 ml. Thus, methanol was substituted for dichloromethane.

Epimerization

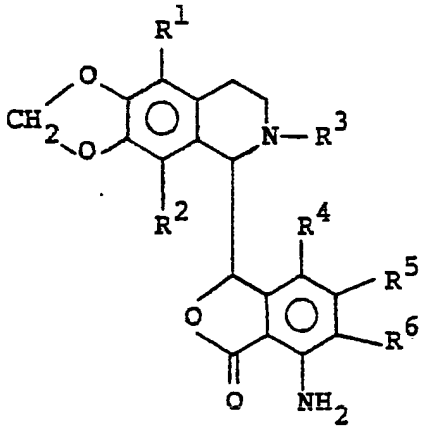
Into a glass reaction vessel, the obtained methanol slurry containing the amino compound (A-mer content of 46% and B-mer content of 54%) and 4.4 g of sodium hydroxide were charged. After the reaction was carried out at 60°C under stirring for 10 hours, the mixture was filtered to recover the crystal of A-mer.

The resulting reaction mixture contained 23.0 g (content of 96.6%) of A-mer and 0.8 g (content of 3.4%) of B-mer. The solid product obtained by filtration had a purity of about 100%, and the yield of the A-mer was 91% based on the nitro compound used as a starting material.

Thus, tritoqualine (A-mer) which is useful for a drug can be manufactured advantageously and industrially from the trihydroxybenzoic acid as a starting material.

WHAT IS CLAIMED IS

1. A process for preparing 1RS-3'RS epimer of aminophthalideisoquinolines represented by the general formula (I):



(I)

wherein R^1 and R^2 independently represent hydrogen atom or a lower alkoxy group, R^3 is a lower alkyl group, and R^4, R^5 and R^6 independently represent a lower alkoxy group, comprising the steps of :

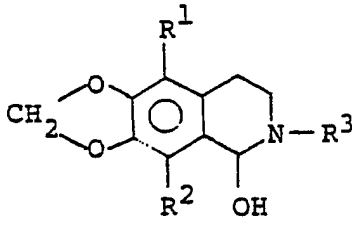
(1) reacting a trihydroxybenzoic acid with a dialkyl sulfate to produce an alkyl ester of a trialkoxybenzoic acid which is then hydrolyzed;

(2) reacting the trialkoxybenzoic acid obtained in the step (1) with formaldehyde;

(3) nitrating the trialkoxyphthalide obtained in the step (2);

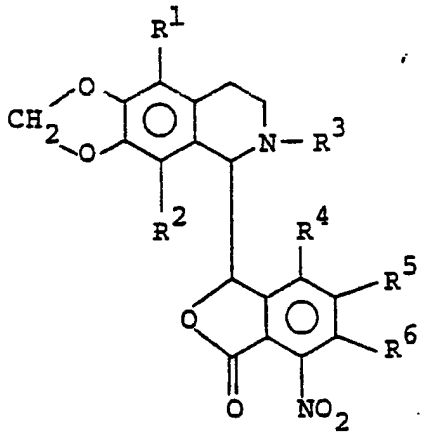
(4) reacting the trialkoxynitrophthalide obtained in the step (3) with an isoquinoline represented by the general

formula (III):



(III)

wherein R^1 to R^3 are as defined above, to produce a nitrophthalideisoquinoline represented by the general formula (II):



(II)

wherein R^1 to R^6 are as defined above; and

(5) either reducing the nitrophthalideisoquinoline followed by epimerization or alternatively epimerizing the nitrophthalideisoquinoline followed by reduction;

characterized in that the reaction of the trihydroxybenzoic acid with the dialkyl sulfate in the step (1) is carried out in an aqueous medium at a pH in the range of from 8.5 to 11, inclusive, with the aid of a caustic alkali.

2. The process as defined in claim 1, wherein the hydrolysis of the alkyl ester of trialkoxybenzoic acid in the step (1) is carried out at a pH of 11 or higher.

3. The process as defined in claim 1, wherein the reaction mixture after the hydrolysis in the step (1) is subjected to acid precipitation at a pH of 4 or lower to collect crystals of the trialkoxybenzoic acid.

European Patent Office

EUROPEAN SEARCH REPORT

Application number 0161499

DOCUMENTS CONSIDERED TO BE RELEVANT

EP 85104478.4

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl 4)
A	GB - A - 873 935 (M. JEANSON.) * Page 1, left column, lines 9-16; fig. 1; claims 4,5; claim 8 * --	1	C 07 D 491/056 A 61 K 31/47
D,A	ANNALEN DER CHEMIE, vol. 763, 1972, Verlag Chemie, Weinheim H. SUGIHARA et al. "Synthese von 2,3-Dimethoxy-5-methyl-1,4-benzochinon und seiner Äthylhomologen" pages 109-120 * Page 111, lines 4-7, formulas * ----	1	

TECHNICAL FIELDS SEARCHED (Int. Cl 4)

C 07 D 491/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	23-07-1985	BRUS

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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E : earlier patent document, but published on, or after the filing date
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